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Original Research

Bridging the Age Gap in breast cancer: Impact of chemotherapy on quality of life in older women with early breast cancer



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KEYWORDS

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Abstract *Introduction:* Older patients with early breast cancer (EBC) derive modest survival benefit from chemotherapy but have increased toxicity risk. Data on the impact of chemotherapy for EBC on quality of life in older patients are limited, but this is a key determinant of treatment acceptance. We aimed to investigate its effect on quality of life in older patients enrolled in the Bridging the Age Gap study.

Materials and methods: A prospective, multicentre, observational study of EBC patients ≥ 70 years old was conducted in 2013–2018 at 56 UK hospitals. Demographics, patient, tumour characteristics, treatments and adverse events were recorded. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires (EORTC-QLQ) C30, BR23 and ELD 15 plus the Euroqol-5D (eq-5d) over 24 months and analysed at each time point using baseline adjusted linear regression analysis and propensity score-matching.

Results: Three thousand and four hundred sixteen patients were enrolled in the study; 1520 patients undergoing surgery and who had high-risk EBC were included in this analysis. 376/1520 (24.7%) received chemotherapy. At 6 months, chemotherapy had a significant negative impact in several EORTC-QLQ-C30 domains, including global health score, physical, role, social functioning, cognition, fatigue, nausea/vomiting, dyspnoea, appetite loss, diarrhoea and constipation. Similar trends were documented on other scales (EORTC-QLQ-BR23, EORTC-QLQ-ELD15 and EQ-5D-5L). Its impact was no longer significant at 18–24 months in unmatched and matched cohorts.

Conclusions: The negative impact of chemotherapy on quality-of-life is clinically and statistically significant at 6 months but resolves by 18 months, which is crucial to inform decision-making for older patients contemplating chemotherapy.

Trial registration number **ISRCTN:** 46099296.

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1. Introduction

Almost half of all breast cancer cases are diagnosed in patients aged ≥ 65 years [1]. Nonetheless, older adults are under-represented in clinical trials [2]. Moreover, standard trial end-points may not be appropriate for older individuals and quality of life (QoL), functional status and cognition may be as important as chance of cure [3]. These knowledge gaps contribute to considerable variation in treatment in this age group [4].

Curative chemotherapy is associated with a survival benefit only in patients with node-positive and oestrogen receptor (ER)–negative disease [5,6]. Older adults have higher risk of treatment toxicities due to comorbidities and reduced organ function, while benefits are mitigated

by competing risks [7]. The impact of chemotherapy on QoL may influence clinicians' and patients' perspectives [8].

Therefore, the effect of anticancer treatments on QoL is essential to inform treatment decisions in this cohort. The CALGB 49907 study documented better QoL for patients aged ≥ 65 receiving capecitabine versus standard regimens, but no QoL differences persisted at 1 year [9]. Patients receiving chemotherapy within clinical trials had better QoL improvements compared with those treated off study [10]. Nonetheless, prospective data on QoL for older patients with early breast cancer (EBC) receiving standard chemotherapy are lacking.

Comorbidities, literacy, symptoms and compliance may influence patient-reported outcomes [11], but the

European Organisation for Research and Treatment of Cancer (EORTC) questionnaires have been validated to evaluate QoL generically in cancer patients [12] and, specifically, in older individuals [13] and in those diagnosed with breast cancer [14].

We aimed to investigate the impact of chemotherapy on QoL in real-world EBC patients aged ≥ 70 recruited to the Bridging the Age Gap study [15]. Matching survival outcomes for the cohort are reported separately.

2. Methods

2.1. Regulatory approval

Ethics approval (IRAS: 12 LO 1808) and research governance approval were obtained. All patients (or their proxies, if cognitively impaired) gave written informed consent.

2.2. Study design

Bridging the Age Gap is a prospective multicentre, observational cohort study. Patients were recruited from 56 UK centres in England and Wales (Table S1). Eligible patients were women ≥ 70 years at diagnosis of operable invasive breast cancer (tumour-node-metastasis stages: T1-3, plus some operable T4b, N0-1, M0). Those unsuitable for surgery or with previous EBC within five years were not eligible.

2.3. Baseline data collection

Patients were recruited at the time of diagnosis and could participate at three levels: full, partial (no requirement to complete QoL assessments) or proxy (simple third-party data collection for those with cognitive impairment).

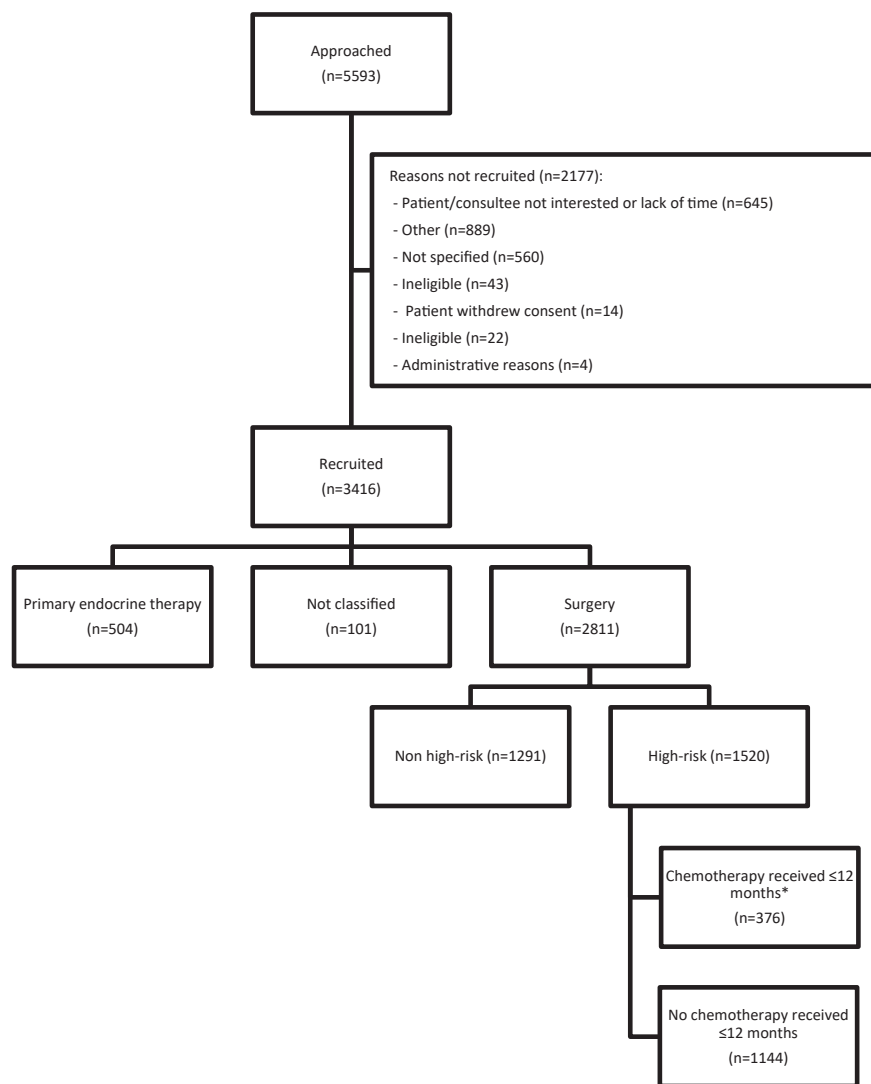


Fig. 1. The STROBE flow diagram for the chemotherapy versus no chemotherapy analyses. * Patients who only received palliative chemotherapy regimens were not counted as having received chemotherapy. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Primary tumour characteristics were collected at baseline. Staging was performed if indicated. Surgery, radiotherapy and systemic treatment data were also collected.

Baseline geriatric assessments included comorbidities (Charlson comorbidity index [CCI]) [16], nutrition (Abridged Patient Generated Subjective Global Assessment [aPG-SGA]) [17–19], functional status (Eastern Cooperative Oncology Group Performance status [ECOG PS], activities of daily living [ADL] [20], instrumental activities of daily living [IADL]) [21], cognition (Mini-Mental State Examination [MMSE]) [22] and medications. Patients were classified as high risk based on ≥ 1 of the following criteria: 1) Human epidermal growth factor receptor type 2 (HER2)-positive status; 2) ER-negative status; 3) grade III; 4) ≥ 1

malignant lymph node; 5) recurrence score (RS) ≥ 30 (Table S2).

QoL was evaluated using four questionnaires. The EORTC-QLQ-C30 includes five functional domains (physical, role, emotional, cognitive and social), nine symptoms (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and global health status [12]. The EORTC-QLQ-BR23 comprises 23 questions evaluating body image, sexual functioning and enjoyment, future perspective, systemic therapy side-effects, breast symptoms, arm symptoms and frustration with hair loss [14]. The EORTC-QLQ-ELD15 contains five scales (functional independence, relationships with family and friends, worries about the future, autonomy and burden of illness) [13]. The EQ-5D-5L was used in this analysis

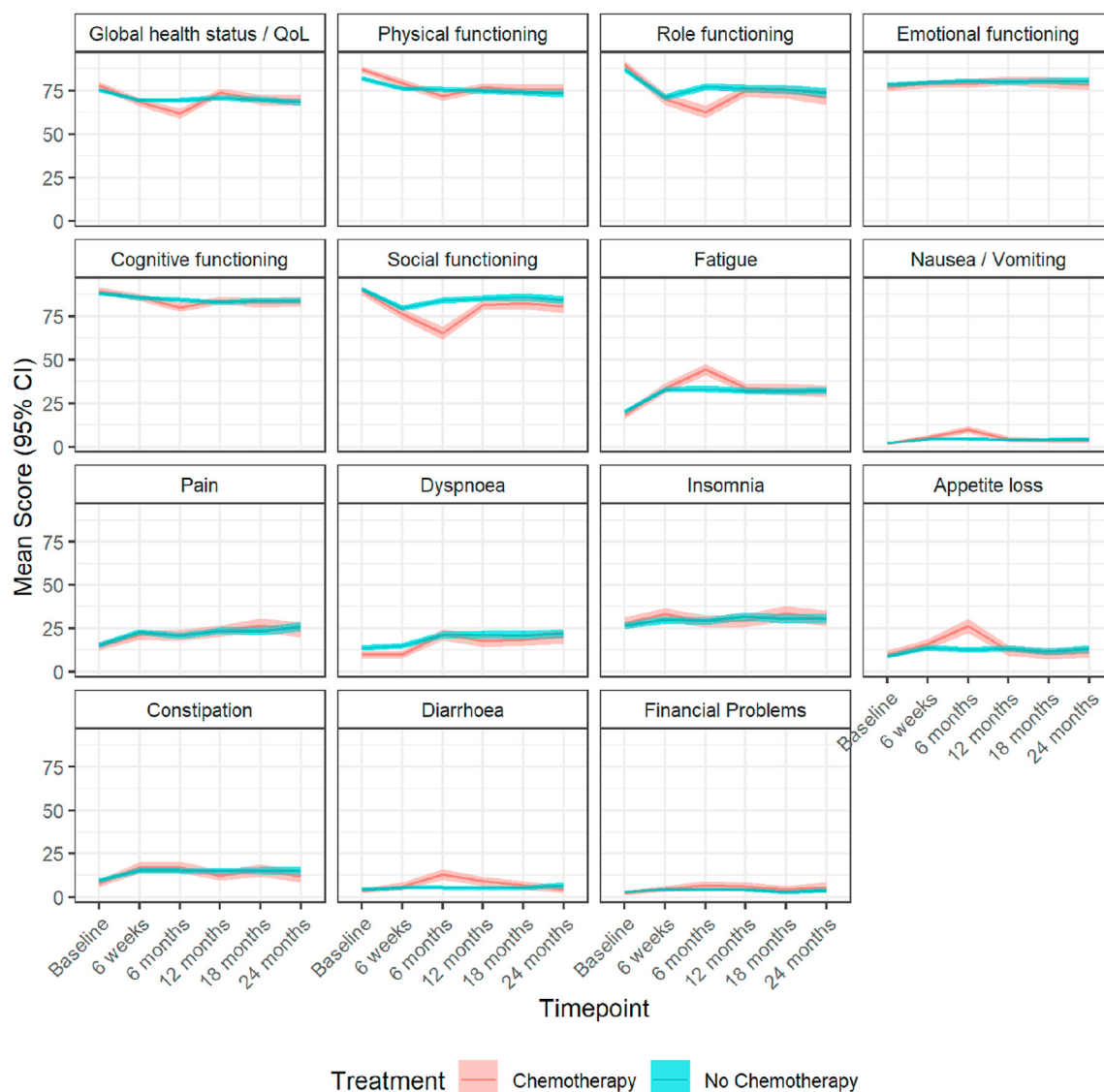


Fig. 2. Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-C30 scale. CI, confidence interval; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires; QoL, quality of life.

Table 1
Baseline postoperative tumour and patient characteristics by receipt of chemotherapy.

Variable	Category	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1144	N = 1520
Participation level	Full	304 (80.9%)	816 (71.3%)	1120 (73.7%)
	Partial	68 (18.1%)	284 (24.8%)	352 (23.2%)
	Consultee	4 (1.1%)	44 (3.8%)	48 (3.2%)
Main side	Right	169 (44.9%)	545 (47.6%)	714 (47.0%)
	Left	207 (55.1%)	599 (52.4%)	806 (53.0%)
Tumour size (mm)	n	375	1143	1518
	Mean (SD)	32.9 (20.7)	29.0 (17.5)	29.9 (18.4)
	Median (IQR)	29.0 (21.0, 40.0)	25.0 (18.0, 35.0)	25.0 (18.2, 36.0)
	Min, Max	0, 210	0, 155	0, 210
Tumour size (mm)	≤20	93 (24.7%)	399 (34.9%)	492 (32.4%)
	21–50	233 (62.0%)	644 (56.3%)	877 (57.7%)
	>50	49 (13.0%)	100 (8.7%)	149 (9.8%)
	Unknown	1 (0.3%)	1 (0.1%)	2 (0.1%)
Grade	Grade I	2 (0.5%)	77 (6.7%)	79 (5.2%)
	Grade II	122 (32.4%)	447 (39.1%)	569 (37.4%)
	Grade III	247 (65.7%)	617 (53.9%)	864 (56.8%)
	Unknown	5 (1.3%)	3 (0.3%)	8 (0.5%)
Histology	Ductal NST	270 (71.8%)	813 (71.1%)	1083 (71.2%)
	Lobular carcinoma	52 (13.8%)	110 (9.6%)	162 (10.7%)
	Tubular carcinoma	0 (0.0%)	5 (0.4%)	5 (0.3%)
	Mucinous carcinoma	1 (0.3%)	13 (1.1%)	14 (0.9%)
	Other	29 (7.7%)	97 (8.5%)	126 (8.3%)
	Unknown	24 (6.4%)	106 (9.3%)	130 (8.6%)
ER positive?	No	132 (35.1%)	240 (21.0%)	372 (24.5%)
	Yes	241 (64.1%)	893 (78.1%)	1134 (74.6%)
	Unknown	3 (0.8%)	11 (1.0%)	14 (0.9%)
HER2 status	Negative	210 (55.9%)	908 (79.4%)	1118 (73.6%)
	Inconclusive	3 (0.8%)	7 (0.6%)	10 (0.7%)
	Positive	159 (42.3%)	173 (15.1%)	332 (21.8%)
	Unknown	4 (1.1%)	56 (4.9%)	60 (3.9%)
Oncotype Dx test performed	No	35 (9.3%)	150 (13.1%)	185 (12.2%)
	Yes	5 (1.3%)	16 (1.4%)	21 (1.4%)
	Not Applicable	252 (67.0%)	434 (37.9%)	686 (45.1%)
	Unknown	84 (22.3%)	544 (47.6%)	628 (41.3%)
Breast surgery	Wide local excision (non wire localised)	113 (30.1%)	412 (36.0%)	525 (34.5%)
	Wire localised wide local excision	43 (11.4%)	150 (13.1%)	193 (12.7%)
	Therapeutic mastoplastic/breast reshaping after WLE	18 (4.8%)	14 (1.2%)	32 (2.1%)
	Mastectomy	186 (49.5%)	549 (48.0%)	735 (48.4%)
	Mastectomy and reconstruction	12 (3.2%)	11 (1.0%)	23 (1.5%)
	Other	4 (1.1%)	8 (0.7%)	12 (0.8%)
Axillary surgery	Axillary sample	11 (2.9%)	38 (3.3%)	49 (3.2%)
	Axillary clearance	136 (36.2%)	247 (21.6%)	383 (25.2%)
	Sentinel lymph node biopsy	200 (53.2%)	725 (63.4%)	925 (60.9%)
	Internal mammary node biopsy	0 (0.0%)	1 (0.1%)	1 (0.1%)
	No axillary surgery	7 (1.9%)	27 (2.4%)	34 (2.2%)
	Unknown	22 (5.9%)	106 (9.3%)	128 (8.4%)
Nodal status	pN0-1mi	175 (46.5%)	508 (44.4%)	683 (44.9%)
	pN1	117 (31.1%)	494 (43.2%)	611 (40.2%)
	pN2	52 (13.8%)	95 (8.3%)	147 (9.7%)
	pN3	32 (8.5%)	46 (4.0%)	78 (5.1%)
	pNx	0 (0.0%)	1 (0.1%)	1 (0.1%)
Nottingham Prognostic Index	n	371	1139	1510
	Mean (SD)	5.1 (1.0)	4.7 (0.9)	4.8 (1.0)
	Median (IQR)	4.9 (4.4, 5.7)	4.5 (4.3, 5.3)	4.6 (4.3, 5.4)
	Min, Max	2.4, 10.2	2.1, 8.1	2.1, 10.2
Age	n	376	1144	1520
	Mean (SD)	73.65 (3.33)	77.97 (5.19)	76.90 (5.14)
	Median (IQR)	73.00 (71.00, 76.00)	78.00 (74.00, 81.00)	76.00 (72.00, 80.00)
	Min, Max	69, 87	69, 95	69, 95
Charlson comorbidity index (no	n	365	1103	1468

(continued on next page)

Table 1 (continued)

Variable	Category	Chemotherapy	No chemotherapy	Total
		N = 376	N = 1144	N = 1520
age)	Mean (SD)	0.79 (1.08)	1.11 (1.38)	1.03 (1.32)
	Median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
	Min, Max	0, 6	0, 9	0, 9
Charlson calculated probability	n	365	1103	1468
	Mean (SD)	0.56 (0.26)	0.43 (0.29)	0.46 (0.29)
	Median (IQR)	0.77 (0.21, 0.77)	0.53 (0.21, 0.77)	0.53 (0.21, 0.77)
	Min, Max	0, 0.77	0, 0.77	0, 0.77
Number of concurrent medications	n	314	1021	1335
	Mean (SD)	3.66 (2.51)	4.30 (2.69)	4.15 (2.66)
	Median (IQR)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	4.00 (2.00, 6.00)
	Min, Max	0, 14	0, 18	0, 18
ADL category	No dependency	303 (80.6%)	760 (66.4%)	1063 (69.9%)
	Mild dependency	33 (8.8%)	146 (12.8%)	179 (11.8%)
	Moderate/severe dependency	16 (4.3%)	136 (11.9%)	152 (10.0%)
	Unknown	24 (6.4%)	102 (8.9%)	126 (8.3%)
IADL category	No dependency	315 (83.8%)	776 (67.8%)	1091 (71.8%)
	Mild dependency	26 (6.9%)	124 (10.8%)	150 (9.9%)
	Moderate/severe dependency	10 (2.7%)	136 (11.9%)	146 (9.6%)
	Unknown	25 (6.6%)	108 (9.4%)	133 (8.7%)
MMSE category	Normal function	342 (91.0%)	1004 (87.8%)	1346 (88.6%)
	Mild impairment	28 (7.4%)	111 (9.7%)	139 (9.1%)
	Moderate impairment	4 (1.1%)	14 (1.2%)	18 (1.2%)
	Severe	2 (0.5%)	15 (1.3%)	17 (1.1%)
APG SGA category	Low	299 (79.5%)	869 (76.0%)	1168 (76.8%)
	Moderate	38 (10.1%)	125 (10.9%)	163 (10.7%)
	High	4 (1.1%)	19 (1.7%)	23 (1.5%)
	Unknown	35 (9.3%)	131 (11.5%)	166 (10.9%)
ECOG performance status	Fully active	296 (78.7%)	740 (64.7%)	1036 (68.2%)
	Restricted in physically strenuous activity	59 (15.7%)	284 (24.8%)	343 (22.6%)
	Ambulatory and capable of all self-care	3 (0.8%)	43 (3.8%)	46 (3.0%)
	Capable of only limited self-care	2 (0.5%)	18 (1.6%)	20 (1.3%)
	Unknown	16 (4.3%)	59 (5.2%)	75 (4.9%)

SD, standard deviation; IQR, interquartile range; NST, no special type; ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; APG SGA, Abridged Patient-Generated Subjective Global Assessment; ECOG, Eastern Cooperative Oncology Group.

to assess overall QoL [23] and individual questions were scored separately from 1 to 5.

Patients were followed up at 6 weeks, 6, 12, 18 and 24 months and QoL and side-effects, based on the Common Terminology Criteria for Adverse Events (CTCAE v4.0), were assessed at each visit.

2.4. Statistical analyses

Analyses were performed in IBM SPSS statistics version 24 and R version 3.6.3 [24,25]. A $p < 0.05$ was considered statistically significant.

The questionnaires were scored according to the EORTC Scoring Manual (3rd Edition) [13]. Missing data were managed accordingly. The analysis included patients with high-risk EBC where QoL questionnaires were available. The mean difference (95% confidence interval [CI]) of the domain scores at each time point, adjusted for baseline scores, was calculated with linear regression models for high-risk participants. Effect sizes after analyses of the EORTC-QLQ-C30 were categorised as either trivial, small, medium or large according to pre-specified thresholds for each domain [26].

The chemotherapy effect on the global health score over time for high-risk patients was estimated using a mixed-effect linear model. The model allowed for time, treatment, treatment–time interaction, and baseline global health status. Differences between the chemotherapy and non-chemotherapy groups were derived at each time point using linear contrasts. The model was fitted to high-risk patients and to the propensity score–matched patients only. For the unmatched analysis the model also adjusted for age and baseline functionality scores.

Propensity score matching was performed to compare the EORTC-QLQ-C30 global health score and the EQ-5D-5L usual activities score in a matched cohort receiving chemotherapy versus patients not receiving it. Logistic regression was used to calculate propensity scores for treatment allocation in high-risk patients. These were used to match chemotherapy patients to those who did not receive chemotherapy based on ADL, IADL, MMSE, ECOG, aPG-SGA, CCI, number of medications and age. The ratio and calliper widths of the propensity scores were chosen based on examination of propensity score overlaps for several combinations of

ratios and callipers. A 1:3 ratio for chemotherapy to no chemotherapy and a calliper of 0.25 times the propensity scores standard deviation was used to optimally match quality and numbers. Participants were matched on the Nottingham prognostic index category (good: ≤ 3.4 , moderate: 3.5–5.4, poor: >5.4) and HER2 status.

3. Results

Between January 2013 and June 2018, 3456 women were recruited from 56 hospitals in England and Wales, and 3416 included in the analysis. 2811/3416 (82.3%) underwent surgery within 6 months of diagnosis, 1520/2811 (54.1%) had high-risk EBC and 376/1520 (24.7%) received chemotherapy (Fig. 1) [27]. The time frames for treatments received in each cohort are shown in Fig. S1 wherein the slight offset in timing of endocrine therapy and radiotherapy between the chemotherapy and no

chemotherapy groups can be seen and should be considered when interpreting the findings.

Patients had a median age of 76.9 years, had a median CCI of 1 (range: 0–9), and took a median of four medications (0–18); 1063 (69.9%) were independent in their ADLs and 1091 (71.8%) in their IADLs, 1346 (88.6%) had a normal MMSE, 1168 (76.8%) had a low aPG-SGA score and 1379 (90.7%) had ECOG PS of 0–1 (Table 1).

Chemotherapy data were available for 360 patients: 124 (34.4%) received anthracycline and taxanes, 119 (33.1%) a taxane alone and 116 (32.2%) an anthracycline alone; one patient received cyclophosphamide, methotrexate, fluorouracil. Three-hundred thirty-two patients (21.8%) had HER2-positive disease: 150 (45.2%) received chemotherapy plus trastuzumab, 13 (3.9%) received trastuzumab alone and 9 (2.7%) chemotherapy alone. EBC was ER-positive in 1134 patients (75.3%), with 1079 (95.1%) receiving endocrine therapy (Fig. S1).

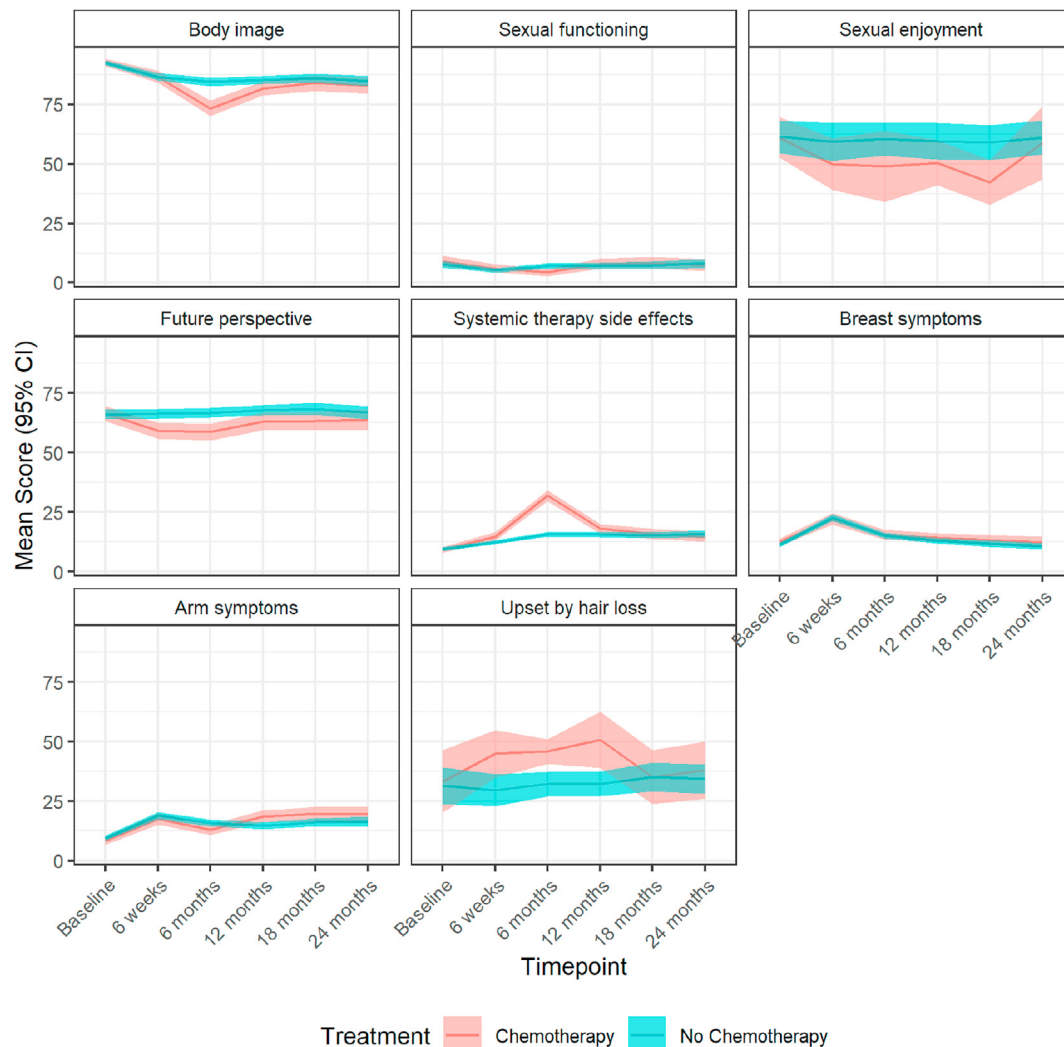


Fig. 3. Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-B23 scale. CI, confidence interval; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires.

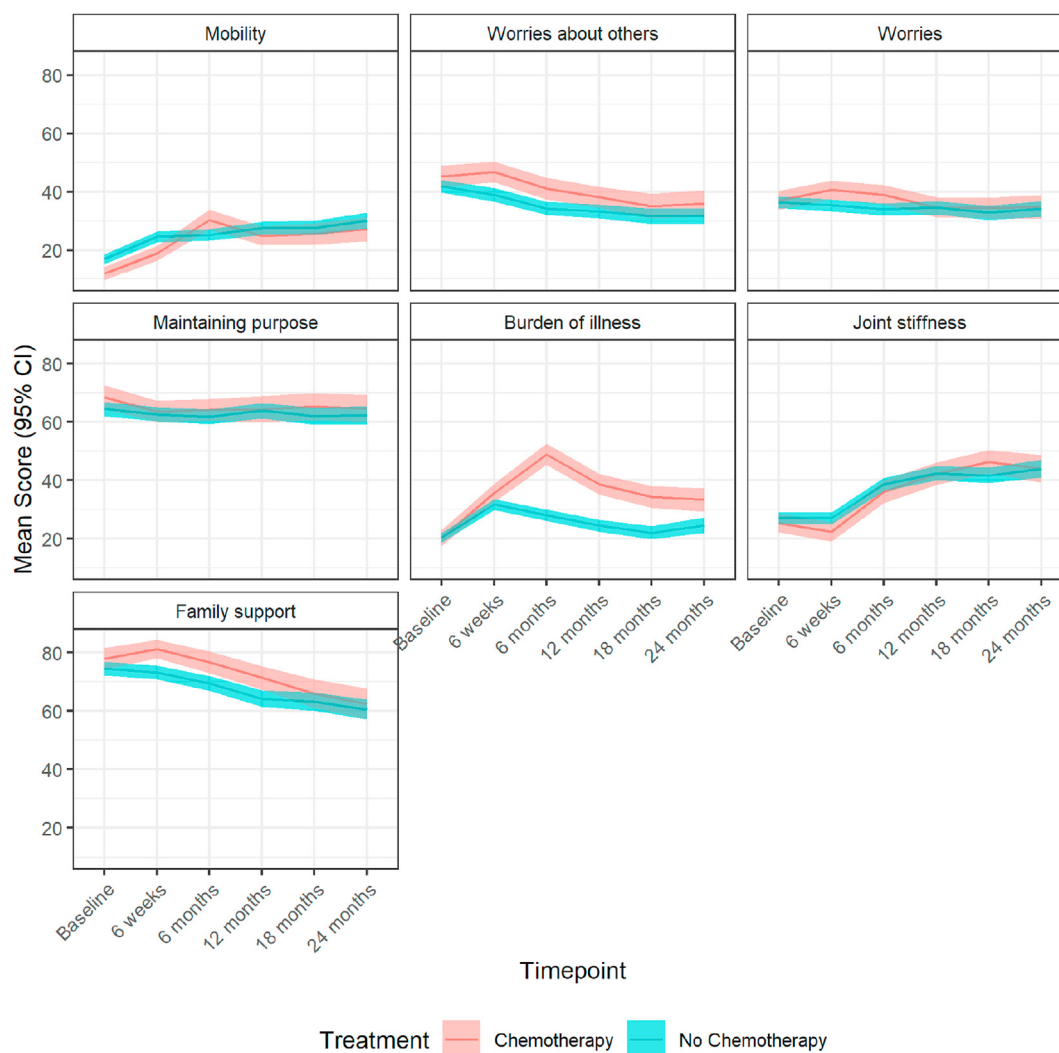


Fig. 4. Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EORTC-QLQ-ELD15 scale. CI, confidence interval; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaires.

Of these high-risk patients, 1120 (73.7%) enrolled with full participation in the protocol (necessary for completion of QoL questionnaires) and 304/1120 (27.1%) had chemotherapy. Figs. S2–S4 and Tables S3–5 show completion rates of QoL questionnaires.

3.1. Impact on QoL domains (EORTC-QLQ-C30)

1049/1120 patients (93.7%) completed the global health-status questions included in the EORTC-QLQ-C30 questionnaire at baseline (Table S6a; Fig. 2). After adjustment for baseline scores, at 6 weeks the differences in the mean scores on some EORTC-QLQ-C30 domains were statistically significant between patients undergoing chemotherapy compared with those of patients not receiving it, including global health (adjusted mean

difference: -2.81 , 95% CI: -5.17 to -0.44 , $p = 0.020$), social functioning (-3.57 , CI: -6.71 to -0.43 , $p = 0.026$) and constipation (3.43 , CI: 0.23 to 6.62 , $p = 0.035$). The impact of chemotherapy remained significant on most domains at 6 months, including global health which was both statistically and clinically significant but small (-9.20 , CI: -11.95 to -6.44 , $p < 0.001$), physical functioning (medium difference: -8.05 , CI: -10.21 to -5.89 , $p < 0.001$), role functioning (small difference: -17.59 , CI: -21.24 to -13.95 , $p < 0.001$), cognitive functioning (small difference: -5.55 , CI: -7.97 to -3.13 , $p < 0.001$), social functioning (large difference: -18.72 , CI: -22.17 to -15.27 , $p < 0.001$), and financial problems (small difference: 3.28 , CI: 1.16 to 5.39 , $p = 0.002$). At 12 months statistically significant differences persisted in physical

functioning (trivial difference: -2.76 , CI -4.95 to -0.57 , $p = 0.014$), role functioning (trivial difference: -4.41 , CI: -8.17 to -0.64 , $p = 0.022$), social functioning (trivial difference: -3.78 , CI: -7.00 to -0.56 , $p = 0.022$), diarrhoea (small difference: 4.15 , CI: 1.62 to 6.68 , $p = 0.001$) and financial problems (trivial difference: 2.50 , CI: 0.27 to 4.73 , $p = 0.028$). Chemotherapy was no longer impactful in any of these domains at 18 and 24 months.

The analyses were repeated on a propensity score-matched subgroup of 410 patients (150 chemotherapy, 260 no chemotherapy) with similar findings (Figs. S5–7; Table S6b).

3.2. Impact on breast cancer-specific QoL domains (EORTC-QLQ-BR23)

1054/1120 patients (94.1%) completed some or all of the EORTC-QLQ-BR23 questionnaire at baseline (Fig. 3;

Table S7). After adjustment for baseline measurements patients given chemotherapy experienced a significant decline of some EORTC-QLQ-BR23 mean scores at 6 weeks compared with those not receiving it in future perspective (adjusted mean difference: -7.20 , 95% CI: -10.72 to -3.68 , $p < 0.001$) and systemic therapy side-effects (3.04 , CI: 1.47 to 4.61 , $p < 0.001$). At 6 months, mean scores were significantly different in future perspectives (-7.54 , CI -11.28 to -3.80 , $p < 0.001$) and systemic therapy side-effects (16.97 , CI: 15.00 to 18.94 , $p < 0.001$). At 12 months, the mean scores between the two groups differed in future perspectives (-4.96 , CI: -8.89 to -1.03 , $p = 0.013$), systemic therapy side-effects (3.32 , CI: 1.41 to 5.22 , $p = 0.001$) and the effect of chemotherapy became significant in arm symptoms (4.94 , CI: 2.18 to 7.69 , $p < 0.001$). At 18 months, the differences remained significant in future perspective (-4.97 , CI: -9.37 to -0.57 , $p = 0.027$) and arm symptoms (3.27 , CI: 0.01 to 6.54 , $p = 0.049$), and at 24

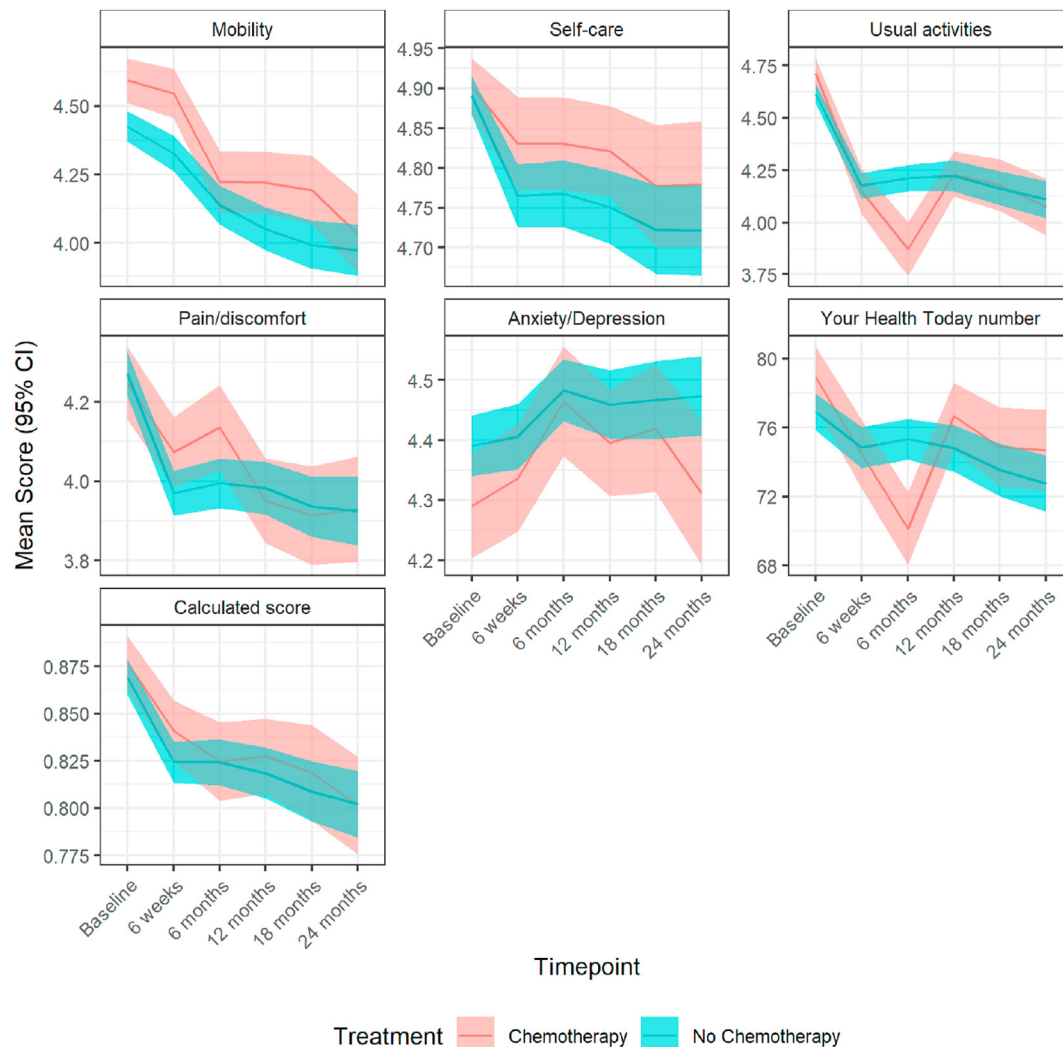


Fig. 5. Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EQ-5D-5L scale. The calculated score is a single summary number (index value) which reflects the health state in the context of the preferences of the general population of a country/region and is derived by applying a formula attaching weights to each of the levels in each dimension as per the EQ-5D-5L User Guide. CI, confidence interval.

months only in arm symptoms (4.02, CI: 0.13 to 7.90, $p = 0.043$).

3.3. Impact on older adults-specific QoL domains (EORTC-QLQ-ELD15)

Some or all of the EORTC-QLQ-ELD15 questionnaire was completed at baseline by 1048/1120 patients (Table S8; Fig. 4). At 6 weeks scores were significantly different between patients given chemotherapy and those not treated in worries about others (adjusted mean difference: 5.31, 95% CI: 1.55 to 9.07, $p = 0.006$), worries (4.09, CI: 0.92 to 7.27, $p = 0.011$) and burden of illness (4.68, CI: 1.25 to 8.11, $p = 0.007$). These differences persisted at 6 months (worries about others [6.19, CI: 2.44 to 9.95, $p = 0.001$]; worries [4.18, CI: 0.89 to 7.46, $p = 0.013$]; burden of illness [21.60, CI: 17.82 to 25.39, $p < 0.001$]; the impact on mobility also became significant (9.82, CI: 6.87 to 12.78, $p < 0.001$). At 12 months, changes remained significant regarding worries about others (4.47, CI: 0.42 to 8.52, $p = 0.031$) and burden of illness (15.21, CI: 11.30 to 19.12, $p < 0.001$), which was the only domain significantly influenced also at 18 months (12.99, CI: 8.81 to 17.17, $p < 0.001$) and 24 months (8.80, CI: 3.93 to 13.66, $p < 0.001$).

Maintaining purpose did not differ throughout the follow-up period, whereas chemotherapy had a positive impact on family support mean scores at 6 weeks (6.21, CI: 2.26 to 10.17, $p = 0.002$), at 6 months (4.91, CI: 0.26 to 9.56, $p = 0.038$) and at 12 months (5.43, CI: 0.39 to 10.46, $p = 0.035$).

3.4. Impact on EQ-5D-5L score and questions

Among the high-risk patients, an EQ-5D-5L score was calculated in 1315 patients (86.5%) at baseline. Health utilities were similar with estimated mean differences less than 0.02 units ($p > 0.1$), whereas the visual analogue scale measures were significantly worse at 6 months in patients receiving chemotherapy versus not (adjusted mean difference: -6.57 , 95% CI: -8.74 to -4.40 , $p < 0.001$). Changes were subsequently no longer significant (Table S9; Fig. 5).

A similar pattern on EQ-5D-5L usual activities score was seen in 520 (118 chemotherapy, 332 no chemotherapy) propensity score-matched patients (Fig. S8).

4. Discussion

This study demonstrates that chemotherapy has both a clinically and statistically significantly negative impact at 6–12 months on several QoL domains (physical, role, cognitive and social functioning, financial problems), symptom scores (fatigue, nausea, dyspnoea, appetite loss, constipation, diarrhoea), and perceived global health. These changes are clinically meaningful and

involve key domains for this population [28] for whom even low-grade toxicities may be challenging [29].

Reassuringly, this effect resolves for most items over 18–24 months, which is consistent with previous QoL data reported in younger cohorts: for example, in 280 EBC patients many domains improved within 12 months after diagnosis, with the exception of cognitive function and financial problems [30], and similar improvements in role functioning were seen in a study of 817 EBC patients [31]. A registry-based analysis documented better physical functioning, role-physical, role-emotional and fatigue scales at 15 years in EBC patients including 46.9% aged ≥ 65 [32]. Similarly, 588 EBC patients enrolled in the Moving Beyond Cancer study had improved physical and psychosocial functioning after radical treatment regardless of chemotherapy use [31]. Neuropsychological analyses also confirmed improving cognitive function during the first four years after radical therapy for EBC [33,34], although data on financial impact are limited [30]. The CANTO study confirmed the transient nature of the impact of chemotherapy on QoL in a large population [35]. Nonetheless, these analyses have either focused on younger patients, where the risk/benefit ratio is different, or addressed the impact of breast cancer treatments (and not specifically of chemotherapy) on QoL in this age group. Our findings are consistent with a previous study in 109 patients aged 70 or older, of whom 57 received adjuvant docetaxel/cyclophosphamide chemotherapy [36].

To our knowledge, this is the largest study to evaluate the impact of contemporary chemotherapy regimens in older adults with EBC in real-world patients. QoL is a meaningful end-point for older patients, who typically derive less survival benefit and increased toxicities on systemic anticancer treatments [37,38]. These benefits need to be carefully balanced with the detrimental impact on QoL and treatment side-effects [39].

Our analysis included baseline geriatric assessments characterising patients in relevant health domains for this age group, such as functional status, comorbidity, cognition, nutrition and concurrent medications which may impact QoL. A comprehensive geriatric assessment can help achieve the required balance between treatment benefits and side-effects and is recommended by guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the International Society for Geriatric Oncology [28,40]. In a randomised study, integrated oncogeriatric care has recently been shown to improve QoL in older patients with cancer being considered for systemic anticancer therapy [41]. Of particular interest was our finding that in patients ≥ 80 the negative impact on QoL does not resolve, which suggests a lack of resilience in this cohort.

The study has several limitations. Selection bias may have influenced our findings despite its inclusive entry criteria and the different levels of participation. The recruited population was slightly skewed

toward younger individuals compared with the general UK EBC patient population [42]. Moreover, we did not include socio-economic factors that might influence frailty nor the effect of endocrine therapy or radiotherapy on QoL, owing to multiple confounders to such an analysis. We did not capture the impact of chemotherapy on QoL outcomes beyond 24 months, and missing data on longitudinal QoL assessments may have influenced findings. Other factors not measured by our analysis may also impact on chemotherapy decisions; therefore, the propensity score matching does not adjust for all differences between the groups. Furthermore, some effects of chemotherapy on QoL documented in our analysis might be statistically significant but not clinically relevant, although for the majority of domains clinically meaningful changes are seen at the six-month time point, which represents the time when most women would have been on chemotherapy. Finally, it was not possible to categorise chemotherapy effects on QoL measured on BR23, ELD15 and EQ-5D-5L domains as thresholds have not been established for these specific tools, and the latter is a utility scale.

In conclusion, our analysis shows that chemotherapy has an impact on several QoL domains in older EBC patients compared with a matched cohort who did not receive cytotoxics. Nonetheless, these effects are temporary and largely resolve within two years. This is essential information for older women to use in decision-making because individualised decisions on treatment options should be based on their values.

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Conflict of interest statement

The authors declare no conflict of interest. Professors Stephen Walters and Thompson Robinson are National Institute for Health Research (NIHR) Senior Investigators; Jenna Morgan is a NIHR Clinical Lecturer; and Kate Lifford is funded by the NIHR as part of this project. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2020.11.022>.

References

- [1] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. 2018. Lyon, France; Available from: <https://gco.iarc.fr/today>.
- [2] Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, et al. Improving the evidence base for treating older adults with cancer: American Society of clinical oncology statement. *J Clin Oncol* 2015;33(32):3826–33.
- [3] Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, et al. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology position article. *J Clin Oncol* 2013;31(29):3711–8.
- [4] Battisti NML, Wallington M, Ring A, Payne S, Birch R, Bomb M, et al. Is age a barrier to chemotherapy? Rates of treatment in older patients treated with breast, colon and lung cancer in England in 2014: a national registry study. *Ann Oncol* 2018;29. p. viii562–viii575.
- [5] Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. *J Clin Oncol* 2006;24(18):2750–6.
- [6] Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the international society of geriatric oncology (SIOG) and European society of breast cancer specialists (EUSOMA). *Lancet Oncol* 2012;13(4):e148–60.
- [7] Kim J, Hurria A. Determining chemotherapy tolerance in older patients with cancer. *J Natl Compr Canc Netw* 2013;11(12):1494–502.
- [8] Ring A, Harder H, Langridge C, Ballinger RS, Fallowfield LJ. Adjuvant chemotherapy in elderly women with breast cancer (AChEW): an observational study identifying MDT perceptions and barriers to decision making. *Ann Oncol* 2013;24(5):1211–9.
- [9] Kornblith AB, Lan L, Archer L, Partridge A, Kimmick G, Hudis C, et al. Quality of life of older patients with early-stage breast cancer receiving adjuvant chemotherapy: a companion study to cancer and leukemia group B 49907. *J Clin Oncol* 2011;29(8):1022–8.
- [10] Mandelblatt JS, Makgoeng SB, Luta G, Hurria A, Kimmick G, Isaacs C, et al. A planned, prospective comparison of short-term quality of life outcomes among older patients with breast cancer treated with standard chemotherapy in a randomized clinical trial vs. an observational study: CALGB #49907 and #369901. *J Geriatr Oncol* 2013;4(4):353–61.
- [11] Scotté F, Bossi P, Carola E, Cudennec T, Dielenseger P, Gomes F, et al. Addressing the quality of life needs of older patients with cancer: a SIOG consensus paper and practical guide. *Ann Oncol* 2018;29(8):1718–26.

- [12] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365–76.
- [13] Johnson C, Fitzsimmons D, Gilbert J, Arraras JI, Hammerlid E, Bredart A, et al. Development of the European Organisation for Research and Treatment of Cancer quality of life questionnaire module for older people with cancer: the EORTC QLQ-ELD15. *Eur J Canc* 2010;46(12):2242–52.
- [14] Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996;14(10):2756–68.
- [15] Collins K, Reed M, Lifford K, Burton M, Edwards A, Ring A, et al. Bridging the age gap in breast cancer: evaluation of decision support interventions for older women with operable breast cancer: protocol for a cluster randomised controlled trial. *BMJ Open* 2017;7(7):e015133.
- [16] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;40(5):373–83.
- [17] Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* 1996;12(1 Suppl):S15–9.
- [18] Read JA, Crockett N, Volker DH, MacLennan P, Choy ST, Beale P, et al. Nutritional assessment in cancer: comparing the mini-nutritional assessment (MNA) with the scored patient-generated subjective global assessment (PGSGA). *Nutr Canc* 2005;53(1):51–6.
- [19] Vigano AL, di Tomasso J, Kilgour RD, Trutschnigg B, Lucar E, Morais JA, et al. The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. *J Acad Nutr Diet* 2014;114(7):1088–98.
- [20] Mahoney FI, Barthel DW. Functional evaluation: the barthel index. *Md State Med J* 1965;14:61–5.
- [21] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179–86.
- [22] Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189–98.
- [23] Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ* 2018;27(1):7–22.
- [24] Team RC. R: A language and environment for statistical computing. 2020. Vienna, Austria; Available from: <https://www.R-project.org/>.
- [25] Corp I. IBM SPSS statistics for windows. Armonk, NY: IBM Corp.; 2016. Version 24.0 ed.
- [26] Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM, et al. Evidence-based guidelines for determination of sample size and interpretation of the European organisation for the research and treatment of cancer quality of life questionnaire core 30. *J Clin Oncol* 2011;29(1):89–96.
- [27] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61(4):344–9.
- [28] Mohile SG, Dale W, Somerfield MR, Hurria A. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology summary. *J Oncol Pract* 2018;14(7):442–6.
- [29] Kalsi T, Babic-Illman G, Fields P, Hughes S, Maisey N, Ross P, et al. The impact of low-grade toxicity in older people with cancer undergoing chemotherapy. *Br J Canc* 2014;111(12):2224–8.
- [30] Hsu T, Ennis M, Hood N, Graham M, Goodwin PJ, et al. Quality of life in long-term breast cancer survivors. *J Clin Oncol* 2013;31(28):3540–8.
- [31] Ganz PA, Kwan L, Stanton AL, Bower JE, Belin TR, et al. Physical and psychosocial recovery in the year after primary treatment of breast cancer. *J Clin Oncol* 2011;29(9):1101–9.
- [32] Klein D, Mercier M, Abeilard E, Puyraveau M, Danzon A, Dalstein V, et al. Long-term quality of life after breast cancer: a French registry-based controlled study. *Breast Canc Res Treat* 2011;129(1):125–34.
- [33] Schagen SB, Muller MJ, Boogerd W, Rosenbrand RM, van Rhijn D, Rodenhuis S, et al. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. *Ann Oncol* 2002;13(9):1387–97.
- [34] Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *J Clin Oncol* 2010;28(29):4434–40.
- [35] Ferreira AR, Di Meglio A, Pistilli B, Gbenou AS, El-Mouhebb M, Dauchy S, et al. Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis. *Ann Oncol* 2019;30(11):1784–95.
- [36] Quinten C, Kenis C, Hamaker M, Coolbrandt A, Brouwers B, Dal Lago L, et al. The effect of adjuvant chemotherapy on symptom burden and quality of life over time; a preliminary prospective observational study using individual data of patients aged ≥70 with early stage invasive breast cancer. *J Geriatr Oncol* 2018;9(2):152–62.
- [37] Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. *Cancer* 2012;118(13):3377–86.
- [38] Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011;29(25):3457–65.
- [39] Wu HS, Harden JK. Symptom burden and quality of life in survivorship: a review of the literature. *Canc Nurs* 2015;38(1):E29–54.
- [40] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32(24):2595–603.
- [41] Soo W-K, King M, Pope A, Parente P, Darzins P, Davis ID. Integrated geriatric assessment and treatment (INTEGRATE) in older people with cancer planned for systemic anticancer therapy. *J Clin Oncol* 2020;38(15_suppl):12011.
- [42] Todd A, Martin C, Morgan J, Herbert E, Bradburn M, Burton M, et al. Age specific recruitment and retention to a large multicentre observational breast cancer trial in older women: the Age Gap Trial. *J Geriatr Oncol* 2020. <https://doi.org/10.1016/j.jgo.2020.10.015>.